REMARKS

The Office Action dated August 20, 2009 has been carefully considered. Claim 1 is amended to clarify that the protecting groups remain coupled until synthesis of the biopolymer array is complete and to further clarify that the on-chip quality control method is practiced while leaving the desired biopolymer array intact on the chip and without a reduction in yield of the synthesized biopolymers. This latter point is particularly significant given that known quality control methods applicable to on-chip synthesis require consumption of all or part of the array or else eliminate detected protected species from further use. Claim 12 is cancelled, and claim 13 is amended to eliminate redundancy. Since the amendment does not involve new matter, entry is believed warranted and is respectfully requested.

Claims 1-3, 13, and 15-22 remain pending and subject to examination.

Rejection under 35 USC §112, second paragraph

Claim 1 and claims dependent therefrom are rejected under 35 USC §112, second paragraph, as being indefinite. Specifically the Examiner notes that the limitation recited as "the nucleotide building blocks" in claim 1 has no antecedent basis. As amended, Applicants have added an antecedent recitation of nucleotide building blocks which overcomes this rejection. Reconsideration is requested.

Rejection under 35 USC §103

The rejection of **claims 1-3, 12, 13, and 15-22** under 35 USC §103(a) as being unpatentable over US Patent No. 6,238,862 to McGall et al (McGall), and Wagner et al (Helvetic Chimica Acta. Vol. 80: 200-212. 1997 (Wagner), in view of US Patent No. 5,151,507 to Hobbs et al (Hobbs) and if necessary, Chen et al (Journal of Organic Chemistry. Vol. 66: 1725-1732; 2001; cited previously) and Agris (PGPUB 20020045167; 4/18/2002; cited previously) is maintained for reasons of record in addition to the reasons set forth below.

According to the Examiner, McGall teaches methods of quality control for manufacturing nucleic acid probe arrays which "reads on" the quality control method of claim 1. McGall assertedly teaches synthesizing nucleic acids using protected monomers such as 5' and 3' protected nucleotides in accordance with step (a) of claim 1 and claim 12. According to the Examiner, the limitation "until synthesis of the biopolymer array" of claim 1 may reasonably be interpreted to mean during any stage of

the "synthesis" of the biopolymer array so that ostensibly McGall's teaching of a single round of synthesis followed by deprotection reads on claim 1.

The Examiner notes that McGall teaches "deprotecting" of the protecting groups at the end of each round of synthesis but further notes that with respect to protected side chains, which would include the base reactive groups, McGall teaches that the side chain protective groups are removed after the desired products are produced, so that the desired product would be the complete oligonucleotide array.

The Examiner also asserts that McGall reads on step (c) of claim 1 with the teaching of "determining the amount of unprotected active sites" (col. 2, lines 49+) by detecting the amount of "detectable labels" on the array (col. 2, lines 40+; cols. 8-9/ Figure 7; especially, col. 9, lines 9+).

The Examiner notes that McGall fails to teach the protecting groups directly coupled to the nucleobase amino groups as required by claim 1 and also notes that McGall fails to teach the limitations of various dependent embodiments.

The Examiner applies Wagner for disclosure of methods of synthesis of various oligonucleotides using protected nucleotides and for teaching that a fluorescent label may be linked directly to the amino group of the nucleobases and for teaching detecting the protecting groups attached to the synthesized oligonucleotides and deprotection of the label attached nucleobase after the synthesis of the oligonucleotide, as well as for disclosure of certain elements recited in dependent embodiments.

Agris is applied for allegedly teaching methods of monitoring the degree of deprotection upon completion of synthesis of oligonucleotides on arrays by detecting detectable protecting groups "on the array" and for teaching that protecting groups may be attached to the nucleotide base through the amino group of the base. The Examiner argues that Agris teaches detecting the degree of deprotection after oligonucleotide array synthesis by measuring the amount of the protecting groups "remaining on the array" and suggests the need for "on-chip detection" so that simple and reliable techniques for determining the purity of the desired oligonucleotides on an array can be achieved. The Examiner notes that Agris uses antibodies to detect protected oligonucleotides in an immunoassay format, which would clearly reduce the yield of oligonucleotide since all those detected in the single detection step are eliminated from downstream uses. The Examiner argues, however, that it would have been obvious to one skilled in the art to substitute the detection method of Wagner (fluroescence detection methods) for the antibody recognition methods of Agris "to achieve the predictable result of detecting the protecting

group remaining attached to the nucleotide bases on the synthesized oligomer array to improve the quality control method for array synthesis."

The Examiner further argues that the motivation to directly detect the remaining detectable protecting group on the side chains to assess "the purity" of the synthesized oligonucleotides comes from Agris' suggestion that there is a need for a simple and reliable technique to control the quality of the synthesized microarray.

With respect to the combination of McGall, Wagner, and Agris, the Examiner submits that the combined disclosures suggest modification of the quality control method of McGall to extend the assessment to protected side chains where the side chains are protected with fluorescent-detectable protecting groups and where deprotection and quality control occurs at the end of synthesis of the array, and further wherein the quality control assessment occurs on-chip and without reduction in yield of biopolymers on the array.

With respect to Applicants' earlier arguments, the Examiner generally argues that Applicants have addressed the references individually whereas it is the combination which teaches all elements of the claimed invention.

This rejection is traversed, and reconsideration is respectfully requested.

Claim 1 is directed to a quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array. The method comprises (a) synthesizing a plurality of desired biopolymer species on an array from monomeric or oligomeric nucleotide building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks, wherein the detectable protecting groups remain coupled until synthesis of the biopolymer array is complete, (b) taking one or more steps to cleave the detectable protecting groups, (c) determining a degree of deprotection by detecting any detectable protecting groups remaining on the array after cleavage, and (d) repeating steps (b) and (c) until detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip and wherein synthesized biopolymer species are not consumed or eliminated by practice of the method.

McGall, on the other hand, only teaches on-chip quality control assessment of degree of deprotection with respect to the terminal reactive hydroxy reactive group, which is involved in the

elongation reaction. As far as protected side chains, included basic reactive groups, McGall makes the single statement that protected side chains are deprotected at the end of synthesis (column 5, lines 8-9). Applicants note that McGall actually fails to teach or suggest any quality control or assessment of deprotection of the protected basic groups located on side chains and fails in fact to acknowledge problems associated therewith, which are the problems addressed and solved by the instant invention. McGall teaches various quality control assessments with respect to on-chip nucleotide synthesis, including efficiency of nucleotide coupling, deprotection of the hydroxy active sites on the free terminal nucleotides, determination of extent of depurination, and determining presence of double-stranded nucleic acids (see leading sentences of paragraphs set forth in summary of invention). However, there is no teaching or suggestion in McGall of quality assessment of deprotection of protected amino groups, which is a well-known and significant problem in oligonucleotide synthesis that is simply not addressed by McGall. The Examiner notes that McGall fails to teach or suggest quality of assessment of deprotection of the basic side chains. Applicants question, therefore, how McGall can serve as the primary reference for finding "obviousness" of the instant claims.

The Examiner asserts Wagner for the disclosure of fluorescent labeling by linking directly to the amino group of nucleobases and for specifically teaching usefulness of the dnseoc group for base protection. Wagner states that it is common knowledge that amino groups of the naturally-occurring 2'-deoxyribonucleotides have to be protected in oligonucleotide synthesis (page 201, Synthesis, first paragraph) and that dnseoc protection is useful for on-support synthesis. However, Wagner stands for the known deficiency in the art overcome by the instant invention. Wagner specifically teaches that after a deprotection step, samples are cleaved from the support, lyophilized, and subjected to quality assessment by reverse HPLC (page 205, lines 5-9). As noted in the instant specification, this consumes product and reduces yield. Wagner does not overcome the deficiencies of McGall with respect to teaching or suggesting on-chip quality control assessment of deprotection of the amine side chains, which is a significant and well known problem in the art. Wagner provides an improved deprotecting treatment but assesses deprotection conventionally.

The Examiner urges that Agris teaches on-chip quality control and may be combined with the methods of Wagner to modify McGall to achieve/obviate the instant methods. Applicants emphatically disagree. There is simply no way to technically combine the methods, and there is simply no motivation to support the importation of individual elements from the teachings of Agris and Wagner into McGall without resort to illicit hindsight reasoning in the form of guidance provided by the instant specification

as to how those elements may be combined to achieve quality assessment and complete on-chip deprotection of protected amine reactive groups without reducing the yield of biopolymer on the array.

Applicants admit that Agris suggests on-support deprotection of amine side chains and on-support quality assessment. Agris, however, employs immunoassays using antibody binding partners specific for any remaining protected groups. Although the antibodies may thereafter be detected in well known immunoassay procedures, the protected oligonucleotides forming immunocomplexes with the detectable antibody may not subsequently be deprotected. Therefore, the Agris methods reduce the yield of synthesized oligonucleotide by the amount of detected protected oligonucleotide. To the extent there is any repetition of steps in the Agris method, they are limited to use of additional antibodies to detect additional remaining protected groups of other species (see, e.g., page 10, column 1, top of page). Paragraphs [0163] through [0173] detail the steps disclosed subsequent to detection of still-protected groups, and Applicants note that all embodiments involve isolating, ignoring, or containing the detected oligos (see in particular [0173]). There is no teaching or enablement of de-complexing the detected oligo for purposes of subjecting it to additional cleavage reactions.

The Examiner urges that the specific method of Agris may be substituted with the method of Wagner and thereafter imported into McGall. However, there is no motivation to modify Agris by replacing the immunoassay with fluorescent labeling without a forethought of importing the combination into McGall, and there is nothing in McGall that would guide a practitioner to be concerned about assessment of the side chain deprotection, since McGall is specifically directed to assessment of deprotection of the hydroxy reactive group implicated in the elongation reaction. Wagner, furthermore, is inapposite to the concept of on-chip quality control. Hence, Applicants submit that without the hindsight guidance provided by the instant invention, a modification of Wagner with Agris results in the use of immunoassay to assess deprotection in place of HPLC to assess deprotection. The Examiner argues that Agris suggests the modification of conducting the methods of Wagner on-chip by noting the efficiency of on-chip purification; however this is very different than on-chip quality control with full retention of yield. Agris teaches a method that provides on-chip purification, but the method involves reduction in yield because it eliminates still-protected oligos. Applicants question where any teaching counter to this is present in Wagner. Indeed, the Wagner method consumes considerable quantities of product in the HPLC assessments disclosed therein but just like Agris can achieve purified product.

The Examiner further urges that the combined method of Agris and Wagner may be imported to modify McGall. First, assuming arguendo that one may even combine Wagner and Agris as suggested by

the Examiner, Applicants strongly counter that there is absolutely no teaching or suggestion in any of the asserted references to make this modification. McGall does not address the problem of side chain protection or deprotection. McGall suggests and teaches quality control assessment of deprotection ONLY of the reactive group involved directly in the elongation reaction. McGall is silent on the issue of quality control of deprotection of side chain groups and only makes a brief mention that any protected side chain groups will be deprotected and the end of synthesis.

Moreover, Applicants submit that the Examiner's rejection analysis is improper under well-established patent law for several reasons. First, the Examiner treats each step of the instant method out of the context of the inventive method as a whole, leading to a long analysis including combinations and motivations set forth for each and every step. In determining the differences between the prior art and the claims, the question under 35 USC §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983). The Examiner argues independent motivations for each step of independent claim 1, which is not a proper §103 analysis under the law and which has resulted in this patchwork amalgam of different combinations of references applied to different steps. Applicants' instant arguments reduce the Examiner's analysis to those points made with respect to three references which are applied for alleged disclosure relating to steps which reflect the critical functional difference between the instant invention and the art.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). However, there must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000). When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself. *ACS Hospital Systems, Inc. v. Montefiore Hospital,* 221 USPQ 929, 933& n.14 (Fed. Cir. 1984). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination *ACS Hospital Systems, Inc. v. Montefiore Hospital,* 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). "Hindsight" reconstruction is engaged in when an implication is made that a word or element describes the "differences", an element

describable by that word is picked from a prior reference, the asserted prior art reference is focused on for that isolated teaching while disregarding, inter alia, how the disclosed element works, and making no finding of a suggestion that items found separately in prior references could or should be combined as in the claim at issue. *See Panduit Corp. v. Dennison Manufacturing Co.*, 1 USPQ2d 1593, 1602 (Fed. Cir. 1987).

Applicants respectfully submit that the Examiner has engaged in illicit hindsight reasoning in combining the McGall, Agris, and Wagner references to achieve the instant invention as defined by claim 1. McGall is not concerned with quality control of deprotection of basic side chains in oligonucleotide on-chip synthesis. McGall is directed to assessment of deprotection of the reactive hydroxy implicated in the elongation reaction. There is no motivation to modify McGall with the teachings of either or both of Agris or Wagner since neither of those references enhances or relates to the motivations of McGall. Further, there is no motivation to combine the teachings of Agris and Wagner. Although Agris teaches on-chip assessment of deprotection, Agris uses an immunoassay format that eliminates the detected oligos from further utility. Wagner employs an off-chip method, HPLC, that also consumes oligo, reducing yield. There is no teaching or suggestion in either reference for using either of the disclosed methods in a manner that retains yield, as provided by the instant invention. Both references teach purification, but both references do so likewise with reduction in yield. Hobbs and Chen, both directed to elements of dependent embodiments, are inapposite to the analysis with respect to claim 1.

Claim 1 and dependent claims 2-3, 13, and 15-22 are therefore nonobvious and patentable under 35 USC §103 over McGall and Wagner in view of Agris, further in view of Hobbs and Chen. Reconsideration is therefore respectfully requested.

Respectfully submitted,

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